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A NEW SYNTHESIS OF THE CORTICOSTEROID SIDE CHAIN

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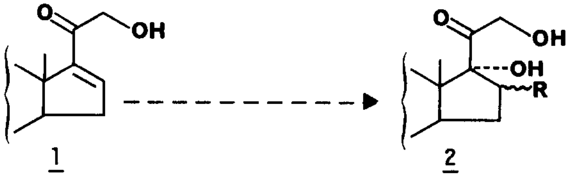
Summary: A short and efficient approach to 3β-acetoxy-21-hydroxypregna-5,16-dien-20-one (6b) has been accomplished using the palladium-catalyzed coupling reaction of 17-enol triflate 3 with α-buthoxyethenyl zinc chloride (8), followed by oxidation of the resultant unsaturated enol ether 4a with m-chloroperbenzoic acid in the presence of potassium acetate.

Following the development of efficient microbial degradation procedures of abundant sterols to 17-oxo-steroids,[1] the transformation of such ketones into pregnane derivatives which would constitute versatile intermediates for the preparation of corticosteroids has become an area of renewed interest.[2]

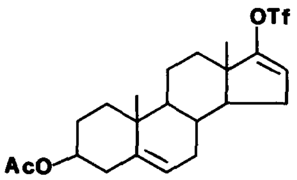
In this connection, enones such as 1 have emerged as valuable synthetic targets since they provide a direct access to the clinically important 16-substituted glucocorticoids 2 (e.g., R=α- or β-Me, α-OH).[2b,2h,3]



An efficient synthesis of 2-alkoxy-1,3-dienes has been recently accomplished by reaction of model enol triflates with alkyl vinyl ethers in the presence of a palladium catalyst.[4]

Given the importance of unsaturated enol ethers 4 as potential precursors of 6b, we were at first attracted by the possibility of exploiting this procedure for a short preparation of 4 from a suitable 17-ketone.

Unfortunately, and in contrast to the model study, the palladium-catalyzed reaction of the easy available enol triflate 3[5] with butyl vinyl ether exhibited little regioselectivity. Depending on the reaction medium and the catalytic system employed, the



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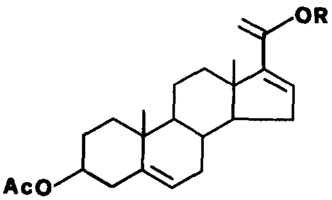
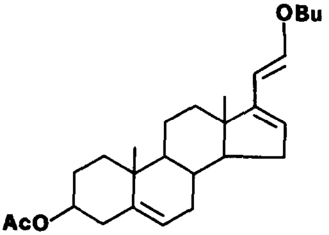


4a, R=Bu
4b, R=Me



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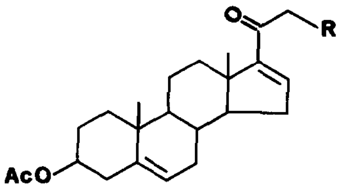
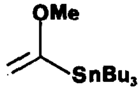


6a, R=H
6b, R=OH



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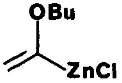

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ratio of α-to β-substituted product (4a:5) ranged from 2.4 to 0.5, a result which made this route synthetically unattractive.

We focused therefore our attention on the stannyl derivative 7,[6] encouraged by the successful attempts to couple aryl and vinyl halides [7] and a 3-triflyloxycephem[8] with (α-ethoxyvinyl)tributyltin.

In fact, coupling between 3 and 7 (1.5 equiv) in the presence of LiCl (3 equiv), $Pd(OAc)_2$ (5 mol%), and PPh_3 (10 mol%) in DMF at 60°C for 4.5 h afforded, after basic workup[9] and chromatography on basic Woelm alumina (activity II; hexane/CH_2Cl_2/Et_3N = 75/25/1 as eluent), the desired 2-methoxy-1,3-diene 4b[10,11] in 54% yield.

Even more gratifying was however the result obtained when 3 was coupled with α-butoxyethenyl zinc chloride (8) using $Pd(PPh_3)_4$ as the catalyst and under conditions analogous to those employed by Hegedus for the palladium-catalyzed coupling of vinyl halides with α-ethoxyethenyl zinc chloride.[12] In this case, the unsaturated enol ether 4a[9,13] was obtained in 82% yield.

Initial attempts to effect oxidation of 4a with m-chloroperbenzoic acid in CH_2Cl_2 in the presence of excess powdered $KHCO_3$ were disappointing, whatever conditions we adopted, and mixtures of 6a and 6b were invariably obtained. Equally ineffective proved to be two-phase procedures (CH_2Cl_2/aqueous $NaHCO_3$),[14] owing to the extreme susceptibility of 4a to acidic hydrolysis.[9] Satisfactorily clean oxidation of 4a did eventually take place as a result of the following procedure. To a stirred solution of 4a (412 mg, 1 mmol) and potassium acetate (490 mg, 5 mmol) in MeOH/CH_2Cl_2= 4/1 (15 ml) was added 85% m-chloroperbenzoic acid (190 mg, 1.1 mmol) in small portions over a 5 min period at 0°C. After stirring for 0.5 h at 0°C, 2N HCl (2.6 ml) was added and stirring was continued for additional 15 min at 0°C. The reaction mixture was then diluted with saturated $NaHCO_3$ and extracted with CH_2Cl_2. The organic phase was washed with brine, dried (Na_2SO_4), and evaporated. Chromatography of the residue (436 mg) on silica gel (15 g) with hexane/AcOEt = 8/2 as eluent afforded 6b (250 mg, 67%).[15,16] The efficient construction of the 21-hydroxy- Δ^{16}-20-keto moiety from 17-ketones is thus completed.

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11. 4b: mp 116-119°C (MeOH, 1 drop Et_3N, lit.[10] mp 115-120°C); $[\alpha]_D$ ($CHCl_3$/pyridine = 9/1, 1%) -58°; IR (KBr) 1736 (C=O) cm^{-1}; ^1H NMR ($CDCl_3/C_5D_5N$ = 9/1) δ 0.93 (3H, s, 13-Me), 1.03 (3H, s, 10-Me), 2.00 (3H, s, 3β-OAc), 3.57 (3H, s, 20-OMe), 4.07 and 4.28 (2H, 2d, J=1.8 Hz, C-21 H_2), 4.63 (1H, m, 3α-H), 5.40 (1H, m, C-6 H), 6.03 (1H, m, C-16 H).
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16. 6b: mp 172-175°C (MeOH, lit.[15] mp 166-173°C); $[\alpha]_D$ ($CHCl_3$, 1%) -54°; IR (KBr) 3455 (OH), 1706 (acetate C=O), 1673 (ketone C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.96 (3H, s, 13-Me), 1.07 (3H, s, 10-Me), 2.04 (3H, s, 3β-OAc), 3.31 (1H, m, OH), 4.40 and 4.54 (2H, ABq, J=18 Hz, C-21 H_2), 4.60 (1H, m, 3α-H), 5.39 (1H, m, C-6 H), 6.75 (1H, m, C-16 H).

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